Combination of alfuzosin and tadalafil exerts an additive relaxant effect on human prostate

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INTRODUCTION

- Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are highly prevalent in aging men and are strongly linked, independently of age and cardiovascular comorbidities[1].
- Alpha$_1$-adrenergic blockers such as alfuzosin are considered the most effective monotherapy for LUTS suggestive of benign prostatic hyperplasia (BPH)[2].
- Phophodiesterase 5 (PDE5) inhibitors such as tadalafil are the first line treatment for ED[3].
- There is evidence from three recent phase II double-blind placebo-controlled studies that PDE5 inhibitors including tadalafil significantly improve LUTS/BPH[4-6].
- A pilot clinical study also indicates that alfuzosin 10mg once daily in combination with a PDE5 inhibitor (sildenafil 25mg once daily) may be superior to monotherapy to improve both LUTS/BPH and ED[7].
- There is no clinically relevant hemodynamic interaction between alfuzosin 10mg once daily and tadalafil 20mg once daily[8].

AIM OF THE STUDY

- **We aimed to evaluate in vitro the effect of alfuzosin, tadalafil or a combination of both drugs on human prostatic tissue.**

MATERIALS & METHODS

Human prostatic strip preparation

Human prostate samples were obtained from 9 patients undergoing cystoprostatectomy for infiltrating bladder cancer. Prostatic strips were suspended in 5 ml organ chambers filled with Krebs-HEPES buffer containing 118 mM NaCl; 4.7 mM KCl; 1.2 mM MgSO4; 1.2 mM KH2PO4; 2.5 mM $CaCl_2$; 4.2 mM NaHCO3; 11.1 mM glucose, and 20.8 mM HEPES. Indomethacin (10^{-5} M) and dexamethasone (10^{-5} M) were also added to the organ bath throughout the experiments to eliminate possible interferences of cyclooxygenase products or induction of NO-synthase. Organ chambers were maintained at 37°C and continuously bubbled with 95% O2 and 5% CO2 to maintain a pH at 7.4.

In vitro contractile experiments

The tissue preparations were allowed to equilibrate for 60 minutes, while being washed periodically with fresh Krebs-HEPES buffer. Following the equilibration period, the prostatic tissues were primed by the addition to the organ bath of KCl (90 mM, 10 min), washed, and then primed by the addition of norepinephrine (NE) at 10^{-6} M during 5 min. After the priming period, the strips were washed by fresh Krebs-HEPES solution and allowed to re-equilibrate for 20 minutes. Concentration-response curves (CRC) to NE were performed. Then following a 20-min incubation period with either vehicle, tadalafil (10^{-6} or 10^{-5}M), alfuzosin (3.10^{-8}M) or a combination of tadalafil and alfuzosin (10^{-6} +3.10^{-8}M or 10^{-5}+3.10^{-8}M for tadalafil and alfuzosin respectively), CRCs to NE were repeated.

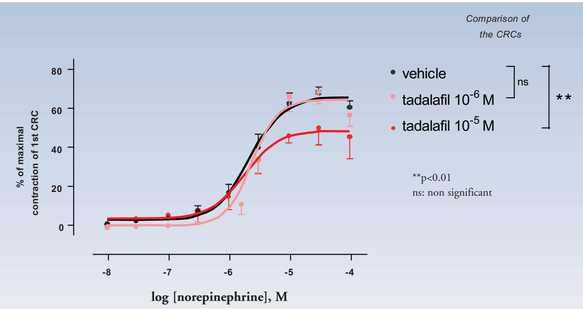
Data Analysis

Results of the second CRC to NE were expressed in percentage of the maximal value obtained during the first CRC. For each CRC in presence of the tested vehicle or compound(s), a pD_2 value (-log concentration of compound that produces 50% reduction of the maximal response) and a mean maximal effect (Emax) were determined using the four-parameter logistic model.

Data were expressed as mean ± SEM for N experiments corresponding to N prostatic samples. Statistical analysis was performed according to the extra sum of squares F test principle with GraphPad Prism® 4.03 software.

RESULTS

Effect of tadalafil on norepinephrine-induced contractions of human prostatic strips

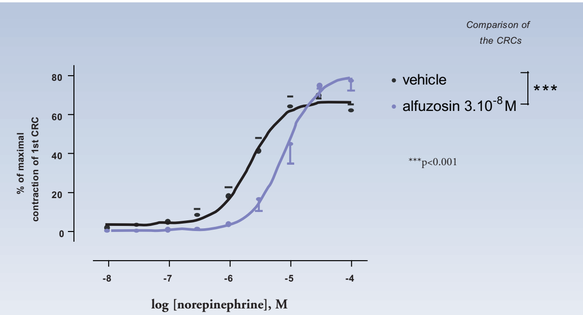


	pD2	*E_{max} (%)*	*N*
vehicle	5.65 ± 0.07	65.43 ± 3.01	9
tadalafil 10^{-6}M	5.57 ± 0.06	64.60 ± 3.28	7
tadalafil 10^{-5}M	5.72 ± 0.16	48.42 ± 4.62*	8

*Comparison of the pD2 or Emax: *p < 0.05, versus vehicle*

- Tadalafil (10^{-5}M) reduced the maximal effect of NE-induced contractions

Effect of alfuzosin on norepinephrine-induced contractions of human prostatic strips



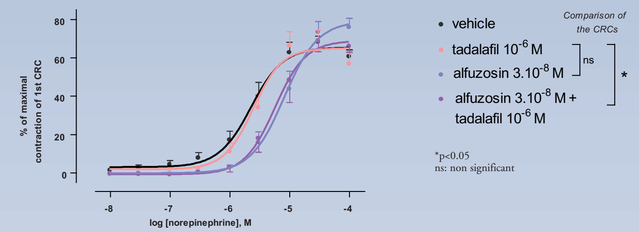
	pD2	*E_{max} (%)*	*N*
vehicle	5.65 ± 0.07	65.43 ± 3.01	9
alfuzosin 3.10-8M	5.09 ± 0.07***	79.20 ± 5.07*	7

*Comparison of the pD2 or Emax: * p < 0.05, *** p<0.001 versus vehicle*

- Alfuzosin significantly shifted to the right the CRC to NE without reducing the maximal effect, in accordance with its competitive α_1- antagonist pharmacological profile

Effect of the combination of tadalafil and alfuzosin on norepinephrine-induced contractions of human prostatic strips

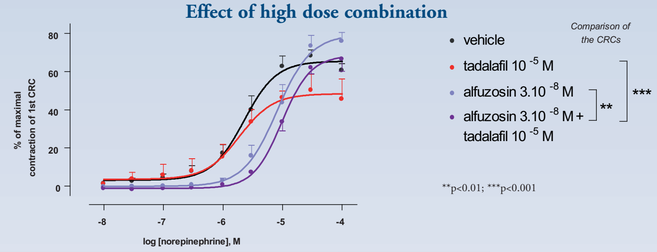
Effect of low dose combination



	pD2	*E_{max} (%)*	*N*
tadalafil 10^{-6}M	5.57 ± 0.06	64.60 ± 3.28	7
alfuzosin 3.10^{-8}M	5.09 ± 0.07	79.20 ± 5.07	7
tadalafil 10^{-6}M + alfuzosin 3.10^{-8}M	5.24 ± 0.08*	79.20 ± 5.07	5

*Comparison of the pD2 or Emax: *p < 0.05 versus tadalafil 10^{-6}M*

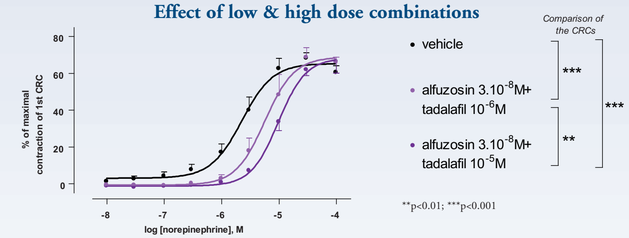
Effect of high dose combination



	pD2	*E_{max} (%)*	*N*
tadalafil 10^{-5}M	5.72 ± 0.16	48.42 ± 4.62	8
alfuzosin 3.10^{-8}M	5.09 ± 0.07	79.20 ± 5.07	7
tadalafil 10^{-6}M + alfuzosin 3.10^{-8}M	5.01 ± 0.04**	68.32 ± 3.06*	7

*Comparison of the pD2 or Emax: *p < 0.05, **p<0.01 versus tadalafil 10^{-5}M*

Effect of low & high dose combinations



	pD2	*E_{max} (%)*	*N*
vehicle	5.65 ± 0.07	65.43 ± 3.01	9
tadalafil 10^{-6}M + alfuzosin 3.10^{-8}M	5.24 ± 0.08***	68.91 ± 4.39	5
tadalafil 10^{-5}M + alfuzosin 3.10^{-8}M	5.01 ± 0.04***##	68.32 ± 3.06	7

*Comparison of the pD2 or Emax: ***p < 0.001 versus vehicle; ## p<0.001 versus tadalafil 10^{-6}M+alfuzosin 3.10^{-8}M*

- The combination of tadalafil (10^{-5}M) and alfuzosin (3.10^{-8}M) exerted a greater inhibitory effect on NE-induced contractions of human prostatic strips compared to tadalafil or to alfuzosin alone
- The effect of the high dose combination was greater than the low dose combination

CONCLUSIONS

- **Alfuzosin and tadalafil exert in vitro an additive inhibitory effect on norepinephrine-contracted human prostatic tissue.**
- **These results support that a combination of tadalafil and alfuzosin could be an effective therapy to treat LUTS associated with BPH.**
- **The value of combining both drugs in BPH patients with LUTS deserves further investigation in placebo-controlled studies.**

(1) Rosen R et al. Eur. Urol. 2003; 44: 637-49. (2) AUA Practice Guidelines Committee. J. Urol. 2006, 170: 530-47. (3) Lue TF et al J. Sex. Med. 2004, 1: 6-23. (4) McVary et al. J. Urol. 2007, 177: 1071-77. (5) McVary et al. J. Urol. 2007, 177: 1401-07. (6) Stief et al. J. Urol. 2007, 177 (suppl.) : pp517, abstract 1565. (7) Kaplan et al. Eur. Urol. 2007, 51: 1717-23. (8) Giuliano F et al. Urology 2006, 67: 1199-1204.